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Original Research

Contribution of alkaline phosphatase in the detection of "Superscan" finding in bone scintigraphy

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Abstract

Aim: Distant osteoblastic bone metastases are frequent manifestations of prostate cancer. Widespread bone metastases can occasionally give rise to uniform distribution of "Tc99m methylene diphosphonate" resulting in a nearly normal appearance on the bone scintigraphy. This situaition is defined as superscan, a finding that can be seen in some malignancies and some metabolic diseases. We think that alkaline phosphatase values, may be a parameter that can prevent erroneous evaluation in prostate cancer patients with extensive bone metastasis,"superscan" finding that can cause an appearance similar to normal bone scintigraphy. This study aimed to investigate the relationship between alkaline phosphatase levels and the superscan finding during the evaluation of bone scintigraphy images.

Material and Methods: Prostate cancer patients who underwent bone scintigraphy in our unit between 2014 and 2022 were retrospectively scanned and those reported as "superscan" were selected. The relationship between serum ALP levels and the "Superscan" finding was evaluated and ROC analysis was performed.

Results: When the bone scintigraphy images of the patients were evaluated, 12 had normal scintigraphy and 12 had superscan findings. While the mean ALP levels of the patients with superscan appearance in the bone scintigraphy were 515.17±476.71, the mean ALP levels of the patients whose bone scintigraphy was reported as normal were calculated as 83.58±25.41 (p=0.005).

Discussion: ALP levels in patients who were reported as superscan during bone scintigraphy were found to be statistically significantly higher than in patients whose bone scintigraphy was reported as normal. Therefore, evaluation of ALP levels while reporting bone scintigraphy examinations by nuclear medicine specialists can greatly prevent false negative results in patients.

Keywords

Prostate Cancer, Bone Scintigraphy, Alkaline Phosphatase, Superscan, Bone Metastases

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Introduction

Prostate cancer is the most common type of cancer among men in the world, with an estimated 1,600,000 cases and 366,000 deaths annually [1]. Distant bone metastases are a frequent manifestation of many types of solid cancers, especially prostate, lung and breast cancers [2]. Due to the high prevalence of bone metastases, treatments are being developed that can prolong life in patients with bone metastases [3-4]. One of the important factors in reducing the quality of life in these patients is bone metastases, especially those that cause pathological fractures [5-6]. Due to the aging of the population, in the coming years, bone metastases will become a probable problem that will constitute an expected healthcare burden in patients with malignancy [7-8]. Osteoblastic lesions in the bones are the most common areas of metastasis in prostate cancer patients. Detection of bone metastases in prostate cancer patients is of great importance in terms of determining treatment management. From the past to the present, technetium-99 radionuclide bone scan has been the most widely used imaging procedure for the diagnosis of bone metastases in prostate cancer, despite its limited sensitivity at PSA levels <10 ng/mL [9].

During normal bone scintigraphy, less than 40% of the Tc-99m hydroxymethylene diphosphonate given intravenously to a patient is retained in the bones, while the majority of the remainder is absorbed by the kidneys [10]. If the bone is very hypermetabolic during this examination, the uptake of the given radiopharmaceutical in the bones is very high compared to the soft tissue and kidneys, and as a result, the amount received from the kidneys is low or lost. Widespread bone metastases can occasionally give rise to a uniform distribution of Tc99m methylene diphosphonate (Tc-99m MDP), resulting in a nearly normal appearance on the bone scan [11]. In bone scintigraphy, faint or absent kidney and soft tissue activity and intense symmetrical diffuse markedly increased activity uptake in the bones relative to soft tissues is defined as a superscan, a finding that can be seen in some malignancies and some metabolic diseases [12]. This situation can be observed especially in prostate and breast cancer, as well as in lymphomas [13]. Metastatic carcinoma of the prostate is one of the most common causes of a malignant superscan and approximately 15% of prostate cancer patients may have a "superscan" image during diagnosis or follow-up [14]. Superscan may also be associated with some metabolic bone diseases. However, the uptake in metabolic bone disease is different from the metastatic state. Radiopharmaceutical uptake in metabolic bone disease is uniform and more in the distal appendicular skeleton. Another feature of metabolic superscan is more intense calvarial uptake than in other parts of the skeleton [15-16]. Diffuse uniform uptake and the absence of focal increased osteoblastic activity in prostate cancer patients with "Superscan" signs may lead to failure to recognize diffuse bone metastases, false-negative results and delayed diagnosis-treatment processes. Failure to recognize the superscan finding in bone scintigraphy examination in prostate cancer patients is a significant error that can have consequences in patient treatment management for diagnosis and treatment. To prevent this, evaluation of the alkaline phosphatase levels should be used to distinguish between a normal patient and the superscan finding. Bone metastases in prostate cancer patients are mostly osteoblastic. We think that alkaline phosphatase values, which are an indicator of bone formation, may be a parameter that can prevent erroneous evaluation in prostate cancer patients with extensive bone metastasis, a "superscan" finding that can cause an appearance similar to normal bone scintigraphy. This study aimed to investigate the relationship between alkaline phosphatase levels and the superscan finding during the evaluation of bone scintigraphy images.

Material and Methods

Patient Population

Prostate cancer patients who underwent bone scintigraphy in our nuclear medicine unit between 2014 and 2022 were retrospectively scanned, and those reported as "superscan" were selected. In this retrospective study, 24 patients diagnosed with prostate adenocarcinoma were included. While 12 of these patients had normal bone scintigraphy findings, 12 patients had a "Superscan" appearance on bone scintigraphy. Medical records, scintigraphy findings and other data of the patients were evaluated retrospectively. The study was carried out with the permission of the Clinical Research Ethics Committee (Date: 2023-03-08, Decision No: 49).

Bone Scintigraphy Protocol

For bone scintigraphy examination, a whole-body scan was performed with a double-headed gamma camera approximately 3 hours after intravenous injection of "Tc-99m Methylene diphosphonate" radiopharmaceutical. Oral hydration was provided to the patients before the examination. Spot images were taken of the required areas and SPECT imaging was performed when necessary. Bone scintigraphy was performed using on average 20 mCi Tc-99m MDP. Bone scintigraphy imaging was performed using the MEDISO AnyScan S gamma camera system (Mediso Medical Imaging Systems Ltd., Budapest, Hungary).

According to bone scintigraphy images, patients were divided into two groups: normal, and superscan. Alkaline phosphatase values were compared between these two patient groups. Bone scintigraphy images were analyzed by an experienced nuclear medicine specialist who was blinded to the clinical details of the patients. Intense and diffusely or heterogeneously increased tracer uptake throughout the skeleton system with markedly diminished or no renal activity and excellent bone details with poor soft tissue uptake were reported as superscan. ALP levels very close to bone scintigraphy in all patients were obtained via the hospital automation system. Serum ALP level reference range was 30-120 U/L.

Statistical Analysis

Analysis was performed using the SPSS Statistical Software program (SPSS version 23.0, SPSS Inc., Chicago). A p-value of <0.05 was considered statistically significant during the tests. When comparing categorical and numerical data, the Independent Student's t-test was used for normally distributed data, and the Mann-Whitney U test was used for the analysis of non-normally distributed data. All continuous variables in the study were described by descriptive statistics such as mean, median, and standard deviation (SD). Categorical

variables were described by frequencies and percentages. ROC curves were used to calculate the serum ALP cutoff levels with maximum sensitivity and specifcity to predict superscan appearance (AUC<0.5, no predictive value; 0.5≤AUC<0.7, less predictive value; 0.7≤AUC<0.9, moderate predictive value; and 0.9≤AUC<1, high predictive value).

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The mean age of the patients was 71.2 ± 8.9 years (range=57-91). When the bone scintigraphy images of the patients were evaluated, 12 had normal scintigraphy and 12 had superscan findings. While the mean ALP levels of the patients with superscan appearance in the bone scintigraphy were 515.17±476.71, the mean ALP levels of the patients whose bone scintigraphy was reported as normal were calculated as 83.58±25.41 (p=0.005) (Table 1). ALP levels were high in 9 (75%) patients with a "Superscan" finding, while ALP levels were within normal limits in 3 patients (25%). ALP levels were high in 1 (8.3%) of patients with normal bone scintigraphy, while ALP levels were within normal limits in 11 patients (91.7%) (Table 2). The mean PSA level in patients with superscan appearance in the bone scintigraphy was 65.36. The mean PSA level inpatients whose bone scintigraphy was reported as normal was 1.12. The ROC curve was used to evaluate the serum ALP level for predicting superscan appearance. The serum ALP level cutoff values (superscan / normal scintigraphic appearance) were 105.50 U/L, with AUC predictive sensitivity and specificity of 0.781, 0.750, and 0.750, respectively. In the ROC analysis performed to determine the superscan appearance of ALP levels, the area under the curve (AUC) was determined to be 0.781 (CI:0.561-1) (p=0.019) (Figure 1).

Table 1. ALP levels in prostate cancer patients with normal bone scintigraphy and bone scintigraphy with superscan findings.

Bone Scintigraphy	ALP Levels	p
Normal	83.58±25.41	0.005
Superscan	515.17±476.71	

Table 2. ALP levels in prostate cancer patients with superscan findings.

ALP Levels	Number	Mean ALP	Range
Elevated	9	668,78	139-1433
Normal	3	54,33	48-67

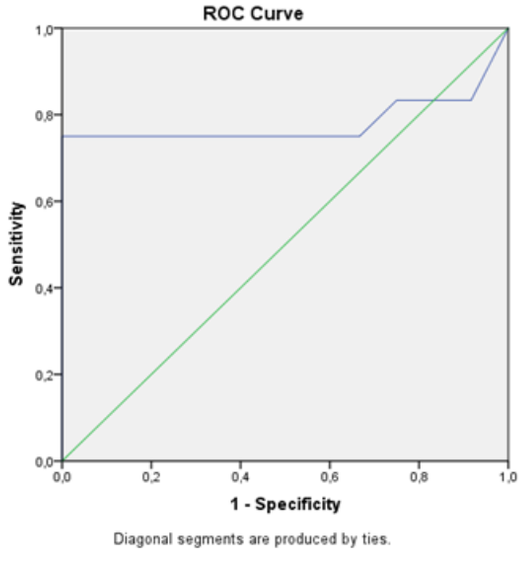

Figure 1. ROC analysis performed to determine the superscan finding with ALP levels.

Discussion

Bone metastases are one of the most important causes of increased morbidity in oncological patients, and detection of bone metastases is very important in determining the treatment plan. Early detection of bone metastases is important in terms of preventing possible complications and thus increasing the quality of life. Bone destruction in bone metastases may occur via osteoclasts, tumor cells, macrophages or monocytes. Bone scintigraphy plays a major role in the detection of bone metastases.

ALP is synthesized by many tissues. Alkaline phosphatase of liver and bone origin accounts for most of the serum alkaline phosphatase level. Bone-derived ALP isoenzyme reflects osteoblastic activity in bone tissue. As a result of increased osteoblastic activity in bone metastases, an increase in serum total ALP and ALP isoenzyme of bone origin is expected.

In the study by Garnero et al., they investigated the role of ALP in the detection of bone metastases in 48 patients with prostate cancer and found that total ALP values were significantly higher in patients with bone metastases [17]. Ramaswamy et al. found that total ALP values were significantly higher in patients with bone metastases in a study involving 62 patients with breast cancer and 30 patients with prostate cancer [18].

Bone scintigraphy with Tc99m-MDP is frequently used in the evaluation of bone metastases due to its high sensitivity, easy and rapid evaluation of the entire skeletal system, and low cost compared to other imaging studies [19]. Bone scintigraphy also can detect bone metastases before anatomical changes occur. Min et al. reported that the specificity (44.1%) in patients who underwent bone scintigraphy alone was lower than the specificity (97.3%) in patients whose ALP level was also evaluated with bone scintigraphy [20].

Although there are publications evaluating the relationship between bone metastases and ALP, there are very few studies evaluating the relationship between superscan finding in bone scintigraphy and ALP. In one of these studies, Manohar et al. scanned bone scintigraphy examinations taken for 5 years in their unit and investigated the ALP values of the patients reported as superscan. In this study, it was found that of 80 patients of superscan, 71 patients (88.7%) had elevated serum ALP levels (normal serum ALP level 45–125 U/L) with a mean serum ALP level of 615.80 U/L [21]. However, no comparison was made with normal bone scintigraphy in this study. At the same time, no statistical data was included and only descriptive analysis was performed.

In our study, the ALP levels in the patients who were reported as superscan during bone scintigraphy were found to be

statistically significantly higher than in the patients whose bone scintigraphy was reported as normal. In addition, a cutoff value was tried to be calculated by performing ROC analysis, although the number of patients was limited.

The first limitation of our study was that the number of patients was partially insufficient. For this reason, we think that it would be more valuable to conduct our study with a larger patient population. Another limitation of our study was that it was conducted retrospectively. We think that the prospective nature of our study will provide additional data.

Conclusion

Prostate cancer continues to be an important cause of morbidity and mortality in male patients, despite a number of new developments in diagnosis and treatment methods in recent years. Bone scintigraphy is an imaging method used to detect bone metastases in patients with prostate cancer. Bone scintigraphy studies have found that the rate of "Superscan" finding in prostate cancer patients can be as high as 23% in some studies [22]. Reporting the "superscan" finding as normal instead of pathological during bone scintigraphy may cause false negative results. In our study, ALP levels in the patients who were reported as superscan during bone scintigraphy were found to be statistically significantly higher than in the patients whose bone scintigraphy was reported as normal. Therefore, evaluation of ALP levels while reporting bone scintigraphy examinations by nuclear medicine specialists can prevent false negative results in patients to a great extent.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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